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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,840	12/31/2001	Xiang-Jin Meng	AM100389	5348

7590 03/18/2004

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EXAMINER	
WORTMAN, DONNA C	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,840	MENG ET AL.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-15 and 17-20* is/are pending in the application.

4a) Of the above claim(s) *4,5,7,17 and 18* is/are withdrawn from consideration.

5)☒ Claim(s) *1* is/are allowed.

6)☒ Claim(s) *3,6,8-15,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,3-15,17-20* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1, 3, 6, 8, 14, and 19 were amended and claims 2 and 16 were cancelled in the response of 26 December 2003. Claims 4, 5, 7, and 17-20 have been withdrawn from consideration as drawn to non-elected inventions. Claims 14, 15, 19 and 20 are now rejoined and under examination since these claims are drawn to the use of an allowable product. Claims 1, 3, 6, 8-15, 19 and 20 are under examination.

Claim 8 is objected to because of the following informalities: Claim 8 is objected to as reciting non-elected subject matter, *viz.*, "(d) an antigenic subunit of avian hepatitis E virus." This subject matter is part of Invention XII as originally set out in the restriction requirement of 15 January 2003. Appropriate correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 6, 8, 14, 15, 19, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is confusing in reciting "An isolated polynucleotide comprising ... (b) the polynucleotide which hybridizes to and which is at least 95% complementary to the nucleotide sequence set forth in SEQ ID NO:1." It is not clear what is intended by "the polynucleotide" since "the" might be thought to refer to a single polynucleotide, but "at least 95% complementary" apparently would encompass a number of different polynucleotides. Claim 3 (b) is also indefinite because it is not clear whether a complementary polynucleotide must hybridize over its entire length to SEQ ID NO:1, or

if hybridization over some portion of its length is sufficient to meet the requirements of the claim.

Claim 6 is indefinite as it recites an immunogenic composition comprising a carrier and a member of an unclear Markush group. It is not clear whether the members of the Markush group are intended to be: (1) an isolated avian hepatitis E virus having the nucleotide sequence set forth in SEQ ID NO:1; (2) its (i.e., SEQ ID NO:1's) complementary strand; and (3) the isolated polynucleotide according to claim 3; or whether the members of the group are intended to be (1) the nucleotide sequence set forth in SEQ ID NO:1; (2) its complementary strand; and (3) the isolated polynucleotide according to claim 3. In the first instance, the claim would encompass an isolated virus vaccine embodiment and two nucleic acid vaccine embodiments, and in the second instance, the claim would encompass three isolated virus vaccine embodiments. Clarification is needed.

Claim 3 is additionally indefinite in reciting "An immunogenic composition comprising ... an isolated avian hepatitis E virus having ... the isolated polynucleotide according to claim 3." First, it is not understood how an isolated virus can have an "isolated" polynucleotide. Second, the Markush group recited in claim 6 is partially redundant since claim 3 recites the same "nucleotide sequence set forth in SEQ ID NO:1 or its complementary strand" as specifically recited again in claim 6.

Claim 8 is indefinite in reciting "an attenuated avian hepatitis E virus having the nucleotide sequence set forth in SEQ ID NO:1 or its complementary strand." Since attenuated viruses are generally mutant viruses, it is not understood how SEQ ID NO:1

can be a common characteristic of all of a modified live, an inactivated, and an attenuated virus.

Claim 14 is confusing because it recites "A method for ... inactivating ... a hepatitis E virus ... comprising passing the pathogenic virus through additional embryonated chicken eggs until said virus is rendered inactivated ..." Since an inactivated virus is non-living, it is not understood how it can be propagated in and recovered from embryonated chicken eggs.

Claim 19 is indefinite because it recites "A method for detecting avian hepatitis E viral nucleic acid sequence ..." but does not recite sufficiently detailed and specific "hybridizing" and "determining" process steps for detecting the specific nucleic acid mentioned in the preamble of the claim. Further, it is not clear how "determining the presence or absence of a hybridized probe complex" correlates with "A method for detecting an avian hepatitis E viral nucleic acid sequence." It is suggested that SEQ ID NO:1 specific limitations from claim 20 be incorporated into the process steps of claim 19, and that "determining the presence or absence of a hybridized probe complex" be amended to read, e.g., "detecting the presence of a hybridized probe complex as an indication of the presence of avian hepatitis E viral nucleic acid."

Claim 20 is indefinite in reciting "nucleic acid probe derived from the nucleotide sequence set forth in SEQ ID NO:1" and "oligonucleotide primers derived from the nucleotide sequence set forth in SEQ ID NO:1" since it is not clear in what sense or to what extent the recited probe and primers are "derived" from the sequence.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition comprising an isolated avian hepatitis E virus having the nucleotide sequence set forth in SEQ ID NO:1, does not reasonably provide enablement for a vaccine comprising isolated avian hepatitis E virus that confers protection against a viral infection or disease, or for a method of vaccination using such a vaccine, or for the nucleic acid vaccine as now recited in claim 8(e). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, essentially for reasons of record in rejecting claims 8-13 in the previous Office action.

Applicant has argued (1) that Fields VIROLOGY, in addition to the passages cited by the Examiner in the previous Office action, also teaches that nonliving virus vaccines can be made and tested by standard techniques to determine their potential disadvantages and advantages, and (2) that making inactivated HEV vaccine and determining whether disadvantages outweigh benefits would be routine experimentation; (3) that one need not know the mechanism of action or the genetic basis of attenuation in order to make and use a viral vaccine without undue experimentation; (4) that Fields refers to successful Jennerian approaches to use an animal or avian virus strain to immunize humans against an antigenically related virus; and (5) that the specification demonstrates that avian HEV is antigenically related to

human HEV, swine HEV, and BLSV. Applicant has (6) cited, and supplied a copy of, Liljeqvist et al. (Journal of Biotechnology 73:1-33, 1999) as evidence of the state of the art for nucleic acid vaccines.

These arguments have been considered but not found persuasive. With respect to (1)-(4) and (6), above, it is agreed that these points are generally true in that techniques and methods are known; however, Applicant has not pointed to any specific teachings in the specification nor any specific factual evidence that these arguments apply to the claimed subject matter, avian HEV, given the state of the art and the unpredictability of the field as discussed in the rejection. It has not been established that vaccination with avian HEV in any form is protective against even avian HEV infection. With respect to point (5), that avian HEV is "antigenically related" to other viruses, animal and human, since it has not been demonstrated that vaccination with avian HEV in any form is protective against avian HEV infection in fowl or other birds, it is not understood how one would be taught to immunize against a different, albeit to some degree related, virus infection in a different host.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. No support could be located for the amendment to claim 8 to the extent that it now recites a nucleic acid vaccine:

"A vaccine ... selected from the group consisting of:

...

(e) a polynucleotide which hybridizes to and which is at least 95% complementary to the nucleotide sequence set forth in SEQ ID NO:1."

Claims 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for propagating a hepatitis E virus having the nucleotide sequence set forth in SEQ ID NO:1 in an embryonated chicken egg, does not reasonably provide enablement for inactivating or attenuating the virus by serially passing the virus through additional embryonated chicken eggs until the virus is rendered inactivated or attenuated. The specification does not teach how to inactivate, or attenuate an avian hepatitis E virus by serially passing it through embryonated chicken eggs. In assessing enablement, it is appropriate to take into account

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

With respect to the state of the prior art, the avian hepatitis E virus disclosed and claimed by Applicant is a newly characterized virus. The direction provided in the

instant specification for inactivating or attenuating the virus is of a general or a prophetic type, including suggesting that both inactivation and attenuation can be achieved by repeated passaging through eggs, and does not involve any actual working examples. The specification does not teach one of skill in the art to produce inactivated virus by serial passage through embryonated chicken eggs since repeated passage requires replicable virus. Making inactivated or attenuated viruses is generally unpredictable, as evidenced by Fields et al., Eds., FIELDS VIROLOGY,Third Edition, Lippincott Williams & Wilkins, 1996. See, for example, page 483, second paragraph, indicating that experimental systems for evaluating attenuations do not exist for every type of virus, and "Basis for Attenuation" which indicates that "satisfactorily attenuated mutants are the product of a process of genetic roulette followed by selection of mutants with the desired properties of attenuation and immunogenicity. The unpredictability of this process is illustrated by the failure of Theiler ... to produce additional attenuated mutants of yellow fever using the protocol that yielded the satisfactorily attenuated 17D strain of virus. The genetic basis for attenuation of measles, mumps, rubella, yellow fever, and vaccinia viruses is unknown, whereas the genetic determinants of attenuation of the three live-poliovirus vaccine strains have been characterized extensively." Taking into account all of the factors listed above, the specification cannot be said to enable one of skill in the art to practice the subject matter of claims 14 and 15 without undue experimentation.

Claim 1 is allowed. Claim 3, if limited to "the nucleotide sequence set forth in SEQ ID NO:1 or its complementary strand," would be allowable.

Because this Office action contains new grounds of rejection not all of which were necessitated by amendment, it is made nonfinal. Any inconvenience to Applicant is regretted.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 571-272-0913. Until 31 March 2004, the examiner can normally be reached on Monday-Thursday, 7:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Primary Examiner
Art Unit 1648

dcw